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10/029,304	12/28/2001	Jonathan A. Ellman	045413/0110	3985

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,304	ELLMAN ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53,55-57 and 60-63* is/are pending in the application.

4a) Of the above claim(s) *56 and 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53,55 and 60-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/9/05 has been entered. Claims 34-37 and 53-59 were pending. Applicants canceled claims 34-37, 54, 56 and 57. In addition, applicants added claims 60-63 and amended claims 53 and 55. Therefore, claims 53, 55-57 and 60-63 are currently pending. Claims 56-57 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 53, 55 and 60-63 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All previous rejections are withdrawn in view of Applicants' arguments and/or amendments.

New Rejections

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 53, 55 and 60-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978)). Applicants' claims are directed to a broad genus of candidate target binding fragments (CTBF's) wherein no structural features are provided for said fragments. In addition, no functional limitations are placed on said fragments either. Applicants' claims state that the CTBF's must bind to a target, but they do not identify the target. In addition, the CTBF's represent merely "candidates" and thus are not even required to bind to said target. Thus, the functional requirement suggested by the term is merely illusory (see also 35 U.S.C. 112, second paragraph rejection below wherein the "size" of the fragments is also noted to be illusory). Thus, Applicants are claiming the entire universe of molecules without exception.

In contrast, Applicants' specification provides only one working example of a CTBF drawn to a cross-linked oxime library that inhibits the interaction between gp120 and CD4 (e.g., see specification, pages 76-84, Example 1).

Applicants are referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding adequate disclosure. For adequate disclosure, like enablement, requires ***representative examples***, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. In addition, when there is ***substantial variation within the genus***, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05). Here, the variation within the genus would be enormous because the CTBF's would encompass every known class and subclass of molecules that could "potentially" interact with every known class and subclass of targets. Furthermore, neither the specification nor the general knowledge of those skilled in the art provide evidence of any partial structure which would be expected to be common to the members of this enormous genus.

Thus, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the claimed invention. The specification and claims do not provide any guidance as to what changes should be made to extend Applicants' one example to the infinite number of possibilities that are currently being claimed. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variable, Applicants' single example is insufficient to describe the enormous genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. *See Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir. 1993); *See also Brenner v. Manso*n, 383 U.S. 519, 535–36, 148 USPQ 689, 696 (1966) (noting, "A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Claims Rejections - 35 U.S.C. § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 53, 55 and 60-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claims 55 and 60-63**, the term "second LG" is vague and indefinite because a "first LG" to which the second LG is presumably compared was never recited in the claims. In addition, Applicants should spell out an abbreviation whenever it first appears in a claim (e.g., see for example, Applicants use of CTBF in the first line of claim 53). In addition, it is not clear how the CTBF-S-S-R^8 can further comprise an LG without destroying the structure of the CTBF-S-S-R^8 (e.g., CTBF-LG-S-S-R^8 or CTBF-S-S-LG-R^8 does not further limit the claim). Furthermore, it is not clear what is being linked to the LG assuming that LG refers to a "linking group" (e.g., is the LG inserted within the CTBF or between the CTBF and the S-S or between the amino portion and the alkyl group in the R^8). Therefore, the metes and bounds of the claimed invention cannot be determined. Applicants are requested to clarify and/or correct.

B. For **claim 53**, the phrase "library comprises two CTBF's that are combined together" is vague and indefinite because it is not clear whether Applicants are referring to the "mixing" of CTBF's members (without covalent bonding) to "combine" said library members in the same reaction vessel or to the "covalent bonding" of CTBF's together (e.g., via disulfide bonding) to "combine" CTBF's into, for example, a "conjugate." If the "conjugate" alternative is possible then it is also unclear whether the library must contain both the conjugate and the CTBF-S-S-R^8 or if the CTBF-S-S-R^8 is somehow transformed into a different molecular structure that is not defined by the claim. Finally, it is also unclear whether the CTBF's have to be bound to each other (e.g., CTBF-CTBF-S-S-R^8). Thus, the metes and bounds of the claimed invention cannot be

determined. Therefore, claim 53 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

C. ***Claims 53 and 60-63*** recite, "... wherein each fragment is a small organic molecule" in line 2. The term "small" is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b). For example, Applicants' specification states, "Candidate target binding fragments that find use herein will generally be less than about 2000 daltons in size ... although organic molecules larger than 2000 daltons in size will also find use herein" (e.g., see specification, page 16, last paragraph). Thus, Applicants specification place no meaningful limits on the size of the fragments because they can be either less than or greater than 2000 daltons in size. Therefore, claims 53, 60-63 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claims Rejections - 35 U.S.C. § 103

5. Claims 53, 55, 60, 62 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirkpatrick et al. (U.S. Patent 6,552,060) (Filing Date is **August 11, 1998**) and Silverman (Silverman, Richard B. The Organic Chemistry of Drug Design and Drug Action. New York: Academic Press, Inc. 1992, pages 19-23, especially Table 2.2).

For ***claims 53, 55, 60, 62 and 63***, Kirkpatrick et al. (see entire document) disclose a library asymmetric disulfides (e.g., see figure 5; see also figures 9-11; see also

paragraph bridging columns 4-5; Table 3; see also column 22; see especially claims 8 and 19; see also column 5, line 5 wherein a straight chain hydroxyalkyl is disclosed; see especially column 5, line 14), which reads on the claimed invention. For example, R_1 and R_2 in this scenario represent the "combined" CTBF's (i.e., R^1 is covalently "combined" together with R^2 via a -SS- linkage to form the asymmetric disulfides R^1-S-S-R^2) that bind to, for example, thioredoxin reductase/thioredoxin targets (e.g., see figure 5; see also columns 7-11; see also figure 9-10; see also column 18, lines 28-36 wherein (bis)disulfides are disclosed). Here, both the R_1 and R_2 CTBF's represent "small organic molecules" (e.g., see Figures 9-11) that are "capable" of being screened in aqueous media (e.g., see figure 5) as required by the specification (e.g., see specification, lines 10-13, "In fact, virtually any small organic molecule that is capable of being chemically coupled to another small organic molecule may find use in the present invention with the provision that it is sufficiently soluble in aqueous solutions to be tested for its ability to bind to a target biological molecule"). Kirkpatrick also disclose that R_1/R_2 can represent linear alkyl groups substituted with -Cl or -OH (e.g., see column 18, lines 28-36, "R_1 and R_2 may be for example any of the substituents shown in Fig. 9 and Fig. 10"; see also figures 9-10, especially figure 9, compound H wherein a linear alkyl substituted with chlorine is disclosed; see also compounds A, B, M and O). Thus, the substituted linear R_1/R_2 groups can represent BOTH the R^8 and the second combined CTBF (i.e., nothing in the claims precludes the R^8 from also representing the second CTBF). Finally, Kirkpatrick et al. also disclose a "library" of asymmetric disulfides (e.g., see Kirkpatrick et al., column 22, paragraph 1, "Using a 96 well plate [i.e., a microtiter plate] format, parallel combinatorial

chemistry ... was used to synthesize a large number of unsymmetrical disulfides [i.e., a library]"; see also column 23, paragraph 1, "A second plate [i.e., microtiter plate] was used for the assessment of biological activity or as a biological screen [i.e., parallel screening using a microtiter plate]"). Although, it us unclear what the "second LG" refers to (e.g., see 35 U.S.C. 112, second paragraph rejection above), Kirkpatrick also disclose an amide for claims (e.g., see figure 9, compound 28), a secondary amine (e.g., see figure 10, compound P) and a second disulfide (e.g., see column 18, line 30 wherein R_1-S-S-Y-S-S-R_2 is disclosed).

The combined prior art teachings of Kirkpatrick et al. differ from the claimed invention as follows:

For ***claims 53, 55, 60, 62 and 63***, Kirkpatrick et al. differ from the claimed invention by not specifically reciting an -NH_2 substituent for the linear R^8 groups. Kirkpatrick et al. only disclose the use of -Cl and/or -OH substituents with "linear" alkyl groups (e.g., see figure 10) and -NH_2 substituents with "branched" alkyl groups (e.g., see claims 8 and 19).

However, Silverman teaches the following limitations that are deficient in Kirkpatrick et al.:

For ***claims 53, 55, 60, 62 and 63***, Silverman (see entire document) teaches the use of "NH_2 substituents" as being "isosteric replacements" for both -Cl and -OH groups (e.g., see Silverman, page 19, section 4 entitled "Bioisosterism"; see also Table 2.2, entry 1a.).

It would have been prima facie obvious to one skilled in the art at the time the invention was made to substitute the -NH_2 group as disclosed by Silverman (e.g., see Silverman Table 2.2, entry 1a wherein -NH_2 is disclosed as a "classic" isostere for -OH and -Cl) for the -Cl and/or -OH substituents on the "linear" asymmetric disulfides as disclosed by Kirkpatrick et al. (e.g., see figure 10, compound H wherein "Cl-CH_2-CH_2-CH_2" is disclosed) because Silverman explicitly state that such substitutions (e.g., NH_2 for OH or NH_2 for Cl) should be made as a result of their similar physical and/or chemical properties (e.g., see Silverman Table 2.2, entry 1a showing equivalence of -OH, -Cl and -NH_2; see also page 19, last paragraph, "Bioisosteres are substituents or groups that have chemical or physical similarities, and which produce broadly similar biological properties"). Consequently, the "Cl-$CH_2CH_2CH_2$" disclosed by Kirkpatrick et al. (e.g., see figure 10, compound H) would have similar chemical and/or physical properties to the same "NH_2-" substituted linear alkyl (i.e., NH_2-$CH_2CH_2CH_2$") according to the teachings of Silverman, which then falls within the scope of the claimed "straight chain alkyl of 1 to 10 carbon atoms that is substituted with an amino" substituent (e.g., see claim 53). A person of skill in the art would have been motivated to make such substitution because Silverman explicitly state that such a substitution is "useful to attenuate toxicity or to modify the activity of a lead compound" (e.g., see Silverman, page 19, last paragraph). Finally, a person of skill in the art would have reasonably expected to be successful because Silverman teach that these are "classic" substitutions that are routinely made by chemists of skill in the art and Kirkpatrick et al. explicitly state

that "linear" alkyl groups (e.g., see Figure 10, compounds A-C) and "amino substituted" alkyl groups (e.g., see claims 8 and 19) are preferred embodiments.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 11, 2005

BENNETT CELSA
PRIMARY EXAMINER